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December 31, 2013

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Office of Office of Pesticide Programs - 7504P
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Attention: 6(a)(2) Administrator

Ref.: **FIFRA 6(a)(2) - Category H-C**

Dear FIFRA Section 6(a)(2) Administrator:

Reckitt Benckiser LLC is submitting the enclosed news item recently brought to our attention. Although we believe the Agency is likely already familiar with the incident described in this news item, in light of guidance provided in PR Notice 98-3 Section XII, we are reporting it out of an abundance of caution and because it is possible that Agency staff would interpret incidents such as the one described to be reportable within the H-C classification.[1]

The news item states that a female patient presented with symptoms that led physicians to suspect that she might be suffering from "[s]urreptitious superwarfarin toxicity." She was treated with Vitamin K and subsequently discharged. Although psychiatry was consulted -- apparently based on a suspicion of intentional ingestion -- the patient denied exposure to anticoagulants, and no identifiable anticoagulants were found during an inspection of her home. Nevertheless, the publication states that 10 days after outside testing and patient discharge a "qualitative brodifacoum drug level" was found to be "positive."

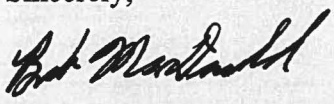
It is important to note that the news item does not specifically attribute any incident to d-CON, or to any rodenticide product. Reckitt Benckiser is not aware of any direct implication of d-CON products being involved in this incident, nor of any attempts by the author of the report to contact its North American headquarters based in Parsippany, NJ prior to publication of this report.

[1] H-C classification may be appropriate, "[i]f the person alleged or exhibited symptoms more pronounced, more prolonged or of a more systemic nature than minor symptoms. Usually some form of treatment of the person would have been indicated. Symptoms were not life threatening and the person has returned to his/her pre-exposure state of health with no additional residual disability." [40 CFR § 159.184 (c)(5)(i)(C)].

P.O. Box 1014
Columbia City, IN 46725
www.srcconsultants.com
Phone: 260-244-6270
Fax: 260-244-6273

If you have any questions, please feel free to contact me.

Sincerely,



Bob MacDonald
Consultant (SRC)
Agent Reckitt Benckiser

Cc: Hal Ambuter
Director, Regulatory and Government Affairs, North America
Reckitt Benckiser LLC

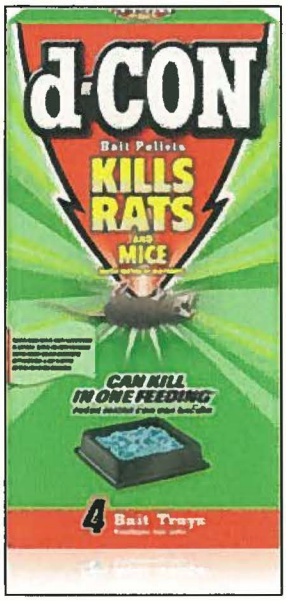
Enclosure -- news item

EMERGENCY MEDICINE NEWS Exclusively for **EM-News.com**: November 18, 2013

The Case Files

Vitamin K-Dependent Factor Activity for Brodifacoum Poisoning

By Andrew M. King, MD; Jeremiah Escajeda, MD; Nathan B. Menke, MD, PhD; Anthony Pizon, MD; Michael Abesamis, MD; and Michael Lynch, MD



A 49-year-old woman presented to our facility as a transfer from an outside hospital with recurrent hematochezia, hematemesis, epistaxis, and ostomy bleeding. Her past medical history was significant for uterine cancer with metastasis to her colon, status post-radiation therapy, and total abdominal hysterectomy approximately three years earlier. She had developed lower gastrointestinal bleeding resulting in diverting colostomy thought to be secondary to radiation proctitis.

The patient reported that she began to develop symptoms five days before presentation to the transferring facility, and staff there noted that she had blood in her ostomy bag and an INR of 16.7; other lab results were PTT 130 sec, PT 163 sec, hemoglobin 7.3 gm/dL, and hematocrit 21.7%. She was transfused six units of FFP and two units of pRBCs, and transferred to our tertiary care facility for further hematologic workup.

The patient's vital signs on arrival to our ICU were blood pressure 109/53 mm Hg, heart rate 79, and 96% on 4L/min nasal cannula. Her initial INR was 1.8, PT 20.0 sec, PTT 37 sec, hemoglobin 7.1 gm/dL, hematocrit 21.9%, and platelet count 158,000. Physical exam revealed diffuse abdominal tenderness without evidence of active gastrointestinal bleeding or epistaxis. The patient denied any exposure or ingestion of warfarin or superwarfarin anticoagulants. Surreptitious superwarfarin toxicity was suspected because of her initial INR elevation, and she was started on IV vitamin K1 at 10 mg daily. Psychiatry was consulted, yet the patient continued to deny superwarfarin exposure. Poison control also performed an inspection of the patient's home, and no identifiable anticoagulants were found.

Her INR was trended daily and peaked at 6.4 on hospital day five. Her vitamin K1 was increased to 60 mg sub-q with the addition of 60 mg PO on that day. Hematologic workup revealed normal PT and PTT mixing studies, thrombin time, fibrinogen level, Dilute Russell's viper venom test, and undetectable anticardiolipin IgM and IgG. Coagulation factor levels V (0.97 U/ml; range 0.70-1.50) and factor VIII (1.33 U/ml; range 0.60-1.50) were normal. Vitamin K-dependent clotting factors II (0.40 U/ml; range 0.70-1.50), VII (0.06 U/ml; range 0.70-1.60), IX (0.07 U/ml; range 0.60-1.50), and X (0.29 U/ml; range 0.70-1.50) were all found to be low, highly suggestive of superwarfarin anticoagulant toxicity.

The patient was then transitioned to 60 mg PO vitamin K1 daily with 60 mg sub-q three times a week to be continued as an outpatient. She was discharged on hospital day nine with an INR of 1.3. A qualitative brodifacoum drug level was subsequently found to be positive by way of high-performance liquid chromatography/tandem mass spectrometry 10 days after outside testing and patient discharge.

Superwarfarins are a group of xenobiotic rodenticides developed in the 1970s to address the genetic resistance to warfarin in rats. (*Clin Toxicol* 2011;49[5]:385.) The most commonly used superwarfarin, brodifacoum, is a 4-hydroxy coumarin with a 4-bromo side chain, which accounts for most human exposures in the United States. (*Clin Toxicol* 2007;45[1]:1; *Arch Intern Med* 1998;158[17]:1929.) Brodifacoum products include Talon-G, Havoc, and D-Con, which are formulated at 0.005% active ingredient. (*Arch Intern Med* 1993;153[16]:1925.)

The superiority of superwarfarins as rodenticides are secondary to higher lipid solubility and concentrations in the liver, making them 100 times more potent than warfarin with a half-life of 10-70 days in humans. (*Arch Intern Med*

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1998;158[17]:1929; *Clin Toxicol* 2011;49[5]:385; *Goldfrank's Toxicologic Emergencies*. Ninth Edition. New York: McGraw-Hill Companies, Inc., pp. 865-9.)

Intestinal and cutaneous absorption can occur. After accumulation in the liver, superwarfarins block hepatic carboxylation of vitamin K-dependent factors (II, VII, IX, and X) by inhibition of the vitamin K 2,3-epoxide reductase enzyme, leading to increased levels of inactive vitamin K epoxide. The resulting coagulopathy induces life-threatening hemorrhage in rodents, humans, and other animals.

Presentation of superwarfarin-induced coagulopathy can include epistaxis, vaginal bleeding, hematuria, gingival bleeding, gastrointestinal bleeding, spontaneous abortion, hemoptysis, and intracranial hemorrhage. (*Arch Intern Med* 1998;158[17]:1929.) Because of brodifacoum's prolonged half-life, single ingestions may result in coagulopathies lasting five to six months. (*Clin Toxicol* 2011;49[5]:385; *Clin Toxicol* 2007;45[5]:487.)

Typically, prolonged, high-dose vitamin K therapy is required in amounts ranging from 15-800 mg/day until adequate superwarfarin elimination is achieved. (*Pharmacotherapy* 2003;23[9]:1186.)

Intentional and unintentional brodifacoum exposures require a high index of suspicion to detect, particularly in cases of surreptitious poisoning. Qualitative and quantitative brodifacoum serum detection tests are available, but they frequently must be sent to outside facilities. Results may take more than seven days, making initiation of long-term vitamin K therapy challenging without a definitive diagnosis.

Vitamin K-dependent coagulation factor activity levels have been shown to be decreased in instances of brodifacoum toxicity. (*J Toxicol Clin Toxicol* 1988;26[3-4]:233; *Conn Med* 2008;72[4]:207; *Am J Emerg Med* 2006;24[3]:383.) Coagulation factor levels can typically be performed at local institutions with results in two to three days. Vitamin K-dependent factor activity measures may serve as a surrogate for detecting superwarfarin poisoning, allowing for earlier initiation of long-term vitamin K therapy.

Brodifacoum-induced coagulopathy may present with a variety of reported clinical manifestations, which in cases of surreptitious exposure, may be particularly challenging to detect, as with our patient. Although a public health concern, brodifacoum poisonings are rarely reported in the literature. (*Clin Toxicol* 2011;49[5]:385.) Early initiation of long-term vitamin K therapy is imperative to prevent recurrent life-threatening hemorrhage because of the prolonged coagulation even after a single exposure or ingestion. (*Ann Emerg Med* 2000;36[3]:262; *Clin Toxicol* 2007;45[1]:1; *Arch Intern Med* 1998;158[17]:1929 and *Arch Intern Med* 1993;153[16]:1925; *Ann Emerg Med* 2002;40[1]:73; *Goldfrank's Toxicologic Emergencies*. Ninth Edition. New York: McGraw-Hill Companies, Inc., pp. 865-9; *Pharmacotherapy* 2003;23[9]:1186.)

Direct serum brodifacoum measures often require lengthy waits for results, and it is often not feasible to wait for results before beginning long-term vitamin K therapy. Our case confirms brodifacoum-induced vitamin K -2,3-epoxide reductase inhibition will demonstrate low coagulation factor II, VII, IX, and X levels while factors VIII and V and thrombin time will remain within normal limits. Coagulation factor assays are readily available at many local hospital laboratory facilities and turnaround time for results are rapid, allowing coagulation factor activity levels to be used to diagnose brodifacoum-induced coagulopathy.

Dr. King *is a medical toxicologist at Children's Hospital of Michigan Poison Control Center, an assistant professor of emergency medicine at Wayne State University, and an emergency medicine attending at Detroit Medical Center.* ***Dr. Escajeda*** *is a third-year emergency medicine resident at the University of Pittsburgh (UP).* ***Dr. Menke*** *is faculty in emergency medicine and toxicology at UP.* ***Dr. Pizon*** *is an associate professor and the chief of the UPMC division of medical toxicology.* ***Dr. Abesamis*** *is an assistant professor and the director of medical toxicology outpatient clinic at UP.* ***Dr. Lynch*** *is an assistant professor of emergency medicine at UP.*

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